UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/556,127	04/20/2000	Ryuichiro Kurane	0163-0758-0X	6027

22850 7590 02/15/2002

OBLON SPIVAK MCCLELLAND MAIER & NEUSTADT PC
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VA 22202

EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	21

DATE MAILED: 02/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/556,127	Kurane et al
Examiner	**Art Unit**
Jeffrey Fredman	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 28, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-45, 47-58, and 60-71* is/are pending in the application.

4a) Of the above, claim(s) *1, 12-14, 16-20, 22, and 27-45* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-11, 15, 21, 23-26, 47-58, and 60-71* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Continued Examination under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e) was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 28, 2002 has been entered.

Claim Objections

2. The objection to claims 25, 26 is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

3. The rejection of claims 50-52, 56-58 and 64-65 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment.

4. Claim 24 and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 24 and 69 are vague and indefinite because the word "robes" appears in line 2. It is likely that this should be corrected to "probes".

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 2, 3, 5, 6, 9, 46, 47 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Horn et al (Nucleic Acids Research (1997) 25(23):4842-4849).

Horn teaches a nucleic acid probe which is labelled with Bodipy FL at the 3' end (see page 4848, column 1, heading "Characterization by hybridization", just below subheading "solution hybridization with fluorometer detection"), and where the probe has a base sequence such that a C is in the 3' terminal position, and also the 4th nucleotide from the 3' position, such that there will inherently be a G residue in the target at the corresponding position upon hybridization. With regard to 3' ends, the probes of Horn are identical in structure to those claimed and disclosed in the specification and therefore inherently meet the extendible limitation as well as the claimed probes. The probes of Horn are chemically modified by the addition of a fluorescent label (page 4848, column 1). Horn expressly recognizes that the probe is quenched upon hybridization (see page 4847, column 2).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 2-9, 23, 24, 47-50, 55, 56, 58, 60-63, 68, 69, 71 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horn (US 2001/0009760 A1, Patent Publication).

Horn teaches a nucleic acid probe which is labelled with Bodipy FL at the 3' end (see figure 8 and page 8, column 1), and where the probe has a base sequence such that a C is in the 3' terminal position, and also the 4th nucleotide from the 3' position, such that there will inherently be a G residue in the target at the corresponding position upon hybridization (see page 8, column 1 for sequence, where underlined sequence is used). With regard to 3' ends, the probes of Horn are identical in structure to those claimed and disclosed in the specification and therefore inherently meet the extendible limitation as well as the claimed probes. The probes of Horn are chemically modified by the addition of a fluorescent label (page 8). Horn expressly recognizes that the probe is quenched upon hybridization (page 8).

Horn expressly teaches use of the method of Figure 3B with a single Bodipy FL probe at the 5' end of the oligonucleotide, stating " This system is illustrated in FIG 3B. In either of these

methods by which the activity of a nucleotide polymerase may be monitored, an oligonucleotide singly labeled with BODIPY FL or other quenchable dye as defined herein at the 5' terminal nucleotide will hybridize to a target sequence and the fluorescence will be quenched without the use of a quencher dye. (Page 10, column 1)". Horn further teaches in figure 3B, the use of an oligonucleotide with three C's at the 2, 3, and 4 positions distant from the 5' end of the oliognucleotide. The primer is necessarily phosphorylated as it can be extended by polymerase (page 10, column 1).

Horn teaches formation of a solid support device (page 9, example 3) and Horn expressly teaches capture of the probes onto solid supports (page 5, column 2) citing the Urdea patent, 5,635,352 for the particular methodologies.

Horn does not teach an oligonucleotide labeled with BODIPY FL at a G or C residue at the 5' end.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to place the BODIPY FL label at a G or C residue on an oligonucleotide such as the BLA3c-PSCPc oligo disclosed on page 8 by Horn because Horn teaches "An oligonucleotide singly labeled with BODIPY FL or other quenchable dye as defined herein at the 5' terminal nucleotide will hybridize to a target sequence and the fluorescence will be quenched without the use of a quencher dye. (Page 10, column 1)." Thus Horn expressly motivates the use of labels on the 5' end and expessly teaches the use of the particular oligonucleotide and an

ordinary practitioner would have been motivated to label the oligonucleotide at the 5' end as expressly suggested by Horn.

10. Claims 2-11, 23, 24, 47-52, 55, 56, 58, 60-65, 68, 69, 71 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horn or Horn (U.S. 2001/0009760 A1) in view of Metelev et al (Bioorganic and Medicinal Chemistry Letters (1994) 4(24):2929-2934).

Horn or Horn (U.S. 2001/0009760 A1) teaches the limitations of claims 2-9, 23, 24, 47-50, 55, 56, 58, 60-63, 68, 69, 71 and 72 as discussed above. Horn or Horn (U.S. 2001/0009760 A1) do not teach the use of 2'-O-methyloligoribonucleotides in a chimeric oligonucleotide probe.

Metelev teaches the use of 2'-O-methyloligoribonucleotides in a chimeric oligonucleotide probe (page 2930, figure 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the probe of Horn or Horn (U.S. 2001/0009760 A1) with the 2'-O-methyloligoribonucleotides of Metelev since Metelev states "In summary, incorporation of 2'-O-methyloligoribonucleotides into PS-oligonucleotides increases nuclease stability and affinity to the target RNA (page 2933).". An ordinary practitioner would have been motivated to make the Horn or Horn (U.S. 2001/0009760 A1) probes chimeric with 2'-O-methyloligoribonucleotides in order to achieve the express advantages of increased nuclease stability and, where needed, increased affinity to RNA.

11. Claims 2-9, 15, 21, 23, 24, 47-50, 53-56, 58, 60-63, 66-69, 71 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horn or Horn (U.S. 2001/0009760 A1) in view of Hogan et al (U.S. Patent 5,030,557).

Horn or Horn (U.S. 2001/0009760 A1) teaches the limitations of claims 2-9, 23, 24, 47-50, 55, 56, 58, 60-63, 68, 69, 71 and 72 as discussed above. Horn or Horn (U.S. 2001/0009760 A1) do not teach the use of helper probes.

Hogan teaches methods for enhancing hybridization including the use of helper probes within ribosomal RNAs (column 4, lines 44-68). Hogan also teaches requirements for helper probes (columns 5 and 6). Hogan also teaches the formation of kits for products of interest (column 14, lines 47-54).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the Horn or Horn (U.S. 2001/0009760 A1) probes with the helper probe and probe methods of Hogan into a kit since Hogan teaches that "Thus, by using a properly selected helper oligonucleotide, the rate of hybridization between the probe and its complementary sequence in the targeted nucleic acid can be substantially increased and even permit hybridization to occur at a rate and under conditions otherwise adequate for an assay where, without the use of the helper, no substantial hybridization can occur.(column 4, lines 36-43). Hogan explicitly states that the helper probe need not be targeted at a unique sequence (column 7, lines 40-42). An ordinary practitioner would have been motivated to form a kit with

the helper probe including the Horn or Horn (U.S. 2001/0009760 A1) in order to increase the rate of hybridization.

12. Claims 2-9, 23-26, 47-50, 55-58, 60-63 and 68-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horn or Horn (U.S. 2001/0009760 A1) in view of Heller et al (U.S. Patent 6,017,696).

Horn or Horn (U.S. 2001/0009760 A1) teach the limitations of claims 2-9, 23, 24, 47-50, 55, 56, 58, 60-63, 68, 69, 71 and 72 as discussed above.Horn or Horn (U.S. 2001/0009760 A1) do not teach the use of a heater to contol probe movement.

Heller teaches the use of temperature for stringency control (column 7, lines 1-5) and Heller teaches the use of electrodes, which when in operation will increase temperature, to control stringency (column 7). Heller further teaches the use of sensors such as thermocouples (column 48).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the probe device of Horn or Horn (U.S. 2001/0009760 A1) with the hybridization control methods of Heller since Heller states "The active nature of the devices provides independent electronic control over all aspects of the hybridization reaction (column 5, lines 64-66)". An ordinary practitioner would have been motivated to control temperature in order to control stringency of hybridization.

Response to Amendment

13. The Declaration under 37 CFR 1.132 filed January 28, 2002 is insufficient to overcome the rejection of the claims based upon 35 USC 102 or 103 as set forth in the last Office action because:

The declaration is not persuasive for two reasons. First, the newly cited art expressly teaches and, for the Horn paper, anticipates the claims. Thus, the unexpected results do not affect this reference, nor the Horn patent publication which teaches the use of the BODIPY-FL probe. Second, the unexpected results include the use of a TMR label. The declaration is unclear as to whether this is BODIPY TMR or simply TMR alone (tetramethylrhodamine). If the TMR is, in fact, BODIPY TMR, then the examiner suggests that the applicant delete BODIPY FL from the claims, and the declaration would be persuasive in allowing the rest of the labels. If the TMR is not BODIPY TMR, then it would support the position that even TMR is equivalent to the BODIPY and Alexa labels and undermine strongly the unexpected nature of the results.

Response to Arguments

14. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the morning are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1637

February 7, 2002